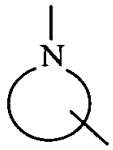
MPEP §2164.04 states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

At page 14, line 1 to page 29, line 12, the Applicants fully disclose the acceptable variants of the R^1, R^2, R^3, A^1, A^2, and A^3 substituents, as well as the substituent of formula:



for use in the present invention. Moreover, at page 4, line 21 to page 13, line 13 and at page 36, line 15 to page 47, line 24, the Applicants provide a detailed explanation of how to make the claimed compounds. The utility of these processes is demonstrated at page 50, line 24 to page 165, line 11 where the Applicants present examples of nearly 250 compounds made by the claimed process. Not only do the Applicants provide adequate disclosure to fully enable the skilled artisan to make the claimed compounds, Applicants have provided a test to enable the skilled artisan to assess the efficacy of the compounds made thereby (page 47, line 31 to page 48, line 17). Applicants also disclose preferred uses of the compounds of the present invention (page 48, line 19 to page 50, line 1). Therefore, the Applicants have met their burden of clearly defining the scope of the claimed compounds, how to make the compounds, and how to use the compounds.

Regarding Claim 17, Applicants submit that platelet aggregation and thrombus formation are widely recognized to be causative of a series of disorders including, restenosis or reocclusion; the thrombus formation in case of vascular surgery, valve replacement,

extracorporeal circulation or transplantation; disseminated intravascular coagulation; thrombotic thrombocytopenic; essential thrombocytosis; and inflammation (page 1, line 21 to page 2, line 10). In rejecting Claim 17, the Examiner asserts that "the examples in the specification do not encompass the entire scope of the Markush groups claimed" (paper number 8, page 5, lines 15-16). Applicants submit that this assertion is entirely without merit. MPEP §2164.02 states:

> The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

As set forth above, Applicants have adequately enabled the present invention and have disclosed how to make and use the compounds of the present invention thereby placing these compounds and their uses in the possession of the skilled artisan without undue experimentation. Despite the lack of a requirement to provide Examples, Applicants have shown that the compounds of the present invention have excellent aggregation inhibition properties (page 47, line 31 to page 48, line 17). In addition, Applicants submit that the objectionable term "prevention" has been removed from Claim 17.

Accordingly, this ground of rejection is unsustainable and should be withdrawn.

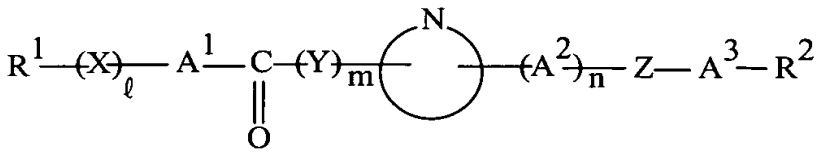
The objection of Claims 1-20 as being drawn to an improper Markush group is respectfully traversed.

Applicants submit that the list of alternative substituents presented in Claim 1, and claims dependent therefrom, are proper. MPEP §2173.05(i) states:

> Where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression.

Applicants submit that the present compounds do share a common nucleus, a β-alanine

derivative of the formula:



Moreover, the diseases of Claim 17 are linked by virtue of a common underlying cause, thrombus formation. Accordingly, the Markush groups of the present invention are proper, and as such this objection should be withdrawn.

The rejection of Claims 1-20 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552

22850

Tel.: 703-413-3000
Fax: 703-413-3220
NFO:VKS
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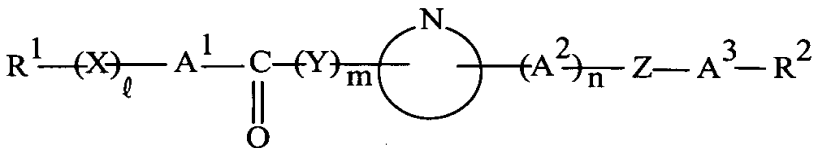
IN THE CLAIMS

Cancel Claim 15.

Amend the claims as follows:

1. (Amended) A compound of the formula:



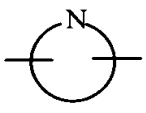
wherein R^1 is a substituted or unsubstituted N-containing cycloalkyl [which may have one or more suitable substituent(s)],

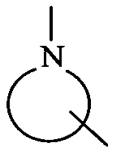
R^2 is carboxy or protected carboxy,

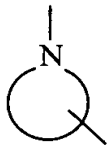
A^1 is a substituted or unsubstituted lower alkylene, a substituted or unsubstituted lower alkanyl-ylidene or a substituted or unsubstituted lower alkenylene [, each of which may have one or more suitable substituent(s)],

A^2 is lower alkylene,

A^3 is a substituted or unsubstituted lower alkylene [which may have one or more suitable substituent(s)],

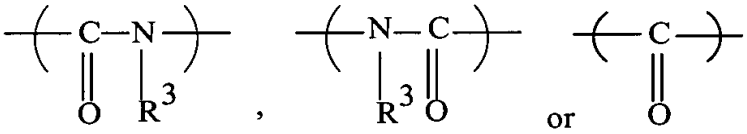
 is a group of the formula:



[(]wherein  is a substituted or unsubstituted N-containing heterocyclic group [which may have one or more suitable substituent(s))],

X is O, S or NH,

Y is NH,

Z is 

[(]wherein R^3 is hydrogen or lower alkyl[)],

ℓ, m and n are each the same or a different [an] integer of 0 or 1,

and a pharmaceutically acceptable salt thereof.

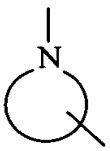
2. (Amended) [A] The compound of claim 1,

wherein R^1 is a substituted or unsubstituted 3 to 8 membered cycloalkyl containing 1 to 3 nitrogen atom(s) [which may have one or more suitable substituent (s)],

R^2 is a carboxy or an esterified carboxy,

A^1 is a substituted or unsubstituted lower alkylene, a substituted or unsubstituted lower alkanyl-ylidene or a substituted or unsubstituted lower alkenylene [, each of which may have one or more suitable substituent(s)],

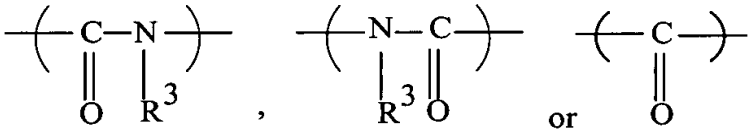
A^2 is lower alkylene,

A^3 is a substituted or unsubstituted lower alkylene [which may have one or more suitable substituent(s)], 

is a substituted or unsubstituted saturated 3 to 8 membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) [which may have one or more suitable substituent(s)], a substituted or unsubstituted unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s) [which may have one or more suitable substituent(s)] or a substituted or unsubstituted saturated 3 to 8-membered heteromonocyclic group containing 1 to 5 carbon atom(s), 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) [which may have one or more suitable substituent(s)],

X is O, S, or NH,

Y is NH,

Z is  or

wherein R^3 is hydrogen or lower alkyl;

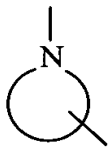
ℓ is an integer of 0 or 1,

m is an integer of 0 or 1,

n is an integer of 0 or 1.

3. (Amended) [A] The compound of claim 2,

wherein R^1 is an unsubsituted piperidyl or a substituted piperidyl containing [which may have] 1 or 2 oxo or [5- (lower) alkyl-2-oxo-l,3-dioxol-4-y1](lower)alkyl,

 is piperidyl, morpholinyl, tetrahydroquinolyl or pyrrolydinyl,

A^3 is an unsubstituted lower alkylene or a substituted lower alkylene containing [which may have] 1 to 3 suitable substituent(s) selected from the group consisting of $(C_1$-$C_6)$alkyl; $(C_2$-$C_6)$alkenyl; $(C_2$-$C_6)$alkynyl; phenyl; phenyl$(C_1$-$C_6)$alkyl; phenyl$(C_1$-$C_6)$alkyl having 1 to 4 $(C_1$-$C_6)$alkoxy, halo $(C_1$-$C_6)$ alkyl or $(C_1$-$C_6)$alkylene dioxy; $(C_1$-$C_6)$alkyl having unsaturated

condensed heterocyclic group containing 1 to 4 nitrogen atom(s); cyano; amino; protected amino; and phenyl(C_1-C_6)alkylcarbamoyl;

R^2, R^3, A^1, A^2, X, Y or Z are each as defined in claim 2,

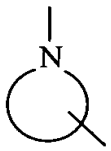
ℓ is an integer of 0,

m is an integer of 0,

n is an integer of 0.

4. (Amended) [A] The compound of claim 3,

wherein R^1 is an unsubsituted piperidyl or a substituted piperidyl containing [which may have] 1 or 2 oxo or [5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl,



is piperidyl, morpholinyl, tetrahydroquinolyl or pyrrolydinyl,

A^3 is an unsubstituted lower alkylene or a substituted lower alkylene containing [which may have] 1 to 3 suitable substituent(s) selected from the group consisting of (C_1-C_6)alkyl; (C_2-C_6)alkenyl; (C_2-C_6)alkynyl; phenyl; phenyl(C_1-C_6)alkyl; phenyl(C_1-C_6)alkyl having 1 to 4 (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl or (C_1-C_6)alkylene dioxy; (C_1-C_6)alkyl having unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s); cyano; amino; (C_1-C_6)alkanoylamino; aroylamino which may have 1 to 3 hydroxy, (C_1-C_6)alkoxy, halogen or phenyl; cyclo(C_3-C_6)alkylcarbonylamino; (C_1-C_6)alkoxy(C_1-C_6)alkylcarbonylamino; (C_2-C_6)carbonylamino; (C_1-C_6)alkylsulfonylamino; phenylsulfonylamino; and phenyl(C_1-C_6)alkylcarbamoyl;

R^2, R^3, A^1, A^2, X, Y or Z are each as defined in claim 3,

ℓ is an integer of 0,

m is an integer of 0,

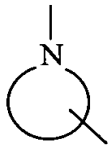
n is an integer of 0.

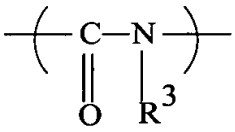
5. (Amended) [A] The compound of claim 4,

wherein R^1 is piperidyl,

A^1 is a lower alkylene or a lower alkanyl-ylidene,

A^3 is an unsubstituted lower alkylene or a substituted lower alkylene containing a [which may have] lower alkyl, a lower alkynyl or a lower alkanoylamino,

 is piperidyl,

Z is  ,

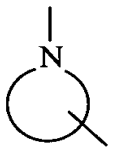
R^2, R^3, A^2, Y, ℓ, m, and n are each as defined in claim 4.

6. (Amended) [A] The compound of claim 5,

wherein R^3 is hydrogen,

A^1 is a lower alkylene,

A^3 is a lower alkylene having a lower alkanoylamino,

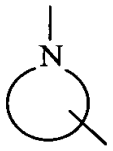
R^1, A^2,  , X, Y and Z are each as defined in claim 5.

8. (Amended) [A] The compound of claim 5,

wherein R^3 is hydrogen,

A^1 is a lower alkylene,

A^3 is a lower alkylene having a lower alkynyl,

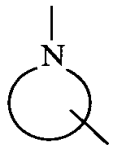
R^1, R^2, A^2,  , X, Y, Z, ℓ, m and n are each as defined in claim 5.

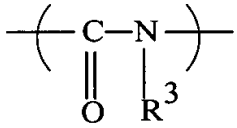
10. (Amended) [A] The compound of claim 4,

wherein R^1 is piperidyl,

A^1 is a lower alkylene or a lower alkanylylidene,

A^3 is an unsubstituted lower alkylene or a substituted lower alkylene containing a [which may have] lower alkyl, a lower alkynyl or a lower alkanoylamino,

 is morpholinyl,

Z is  ,

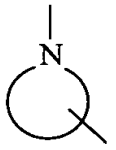
R^2, R^3, A^2, Y, ℓ, m and n are each as defined in claim 4.

11. (Amended) [A] The compound of claim 5,

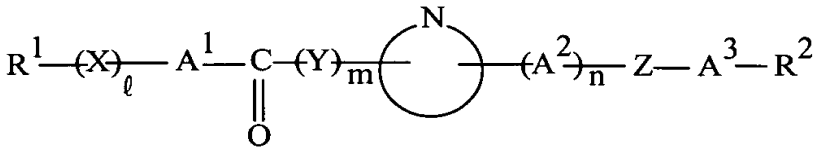
wherein R^3 is hydrogen.

A^1 is a lower alkylene,

A^3 is a lower alkylene,

R^1, A^2,  , X, Y and Z, are each as defined in claim 10.

13. (Amended) A process for preparing a compound of the formula:



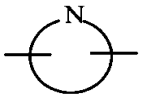
wherein R^1 is a substituted or unsubstituted N-containing cycloalkyl [which may have one or more suitable substituent(s)],

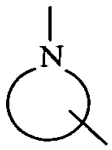
R^2 is a carboxy or a protected carboxy,

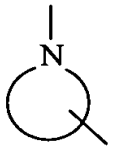
A^1 is a substituted or unsubstituted lower alkylene, a substituted or unsubstituted lower alkanylylidene or a substituted or unsubstituted lower alkenylene [, each of which may have one or more suitable substituent(s)],

A^2 is a lower alkylene,

A^3 is a substituted or unsubstituted lower alkylene [which may have one or more suitable substituent(s)],

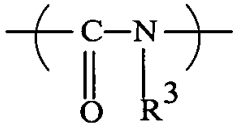
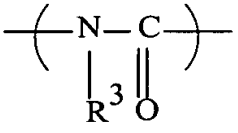
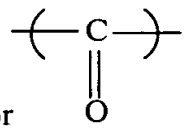
 is a group of the formula:



[(] wherein  is a substituted or unsubstituted N-containing heterocyclic group [which may have one or more suitable substituent(s))],

X is O, S or NH,

Y is NH,

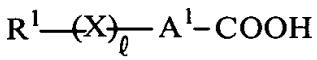
Z is  ,  or 

(wherein R^3 is hydrogen or lower alkyl),

ℓ, m and n are each the same or a different [an] integer of 0 or 1,

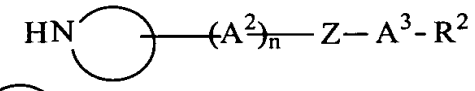
and a salt thereof, which comprises

(i) reacting a compound of the formula



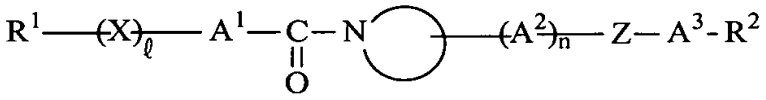
wherein R^1, A^1, X and ℓ are each as defined above, or its reactive derivative at the carboy group

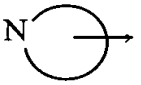
or a salt thereof, with a compound of the formula:



wherein R^2, A^2, A^3,  , Z and n are each as defined above,

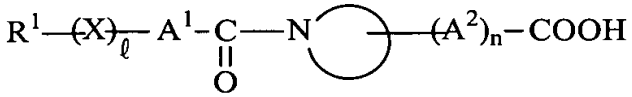
or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula:

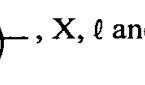


wherein R^1, R^2, A^1, A^2, A^3,  , X, Z, ℓ and n are each as defined above,

or a salt thereof, or

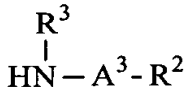
(ii) reacting a compound of the formula:



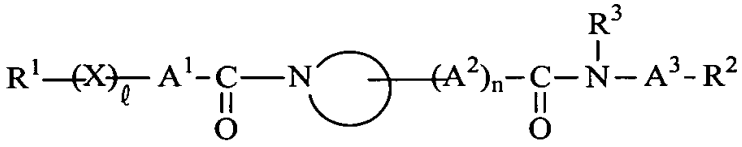
wherein R^1, A^1, A^2,  , X, ℓ and n are each as defined above,

or its reactive derivative at the carboxy group

or a salt thereof, with a compound of the formula:



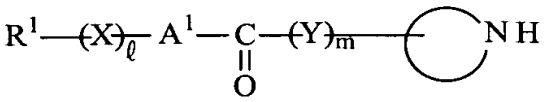
wherein R^2, R^3 and A^3 are each as defined above, or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula:

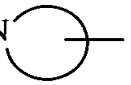


wherein R^1, R^2, R^3, A^1, A^2, A^3,  , X, ℓ and n are each as defined above,

or a salt thereof, or

(iii) reacting a compound of the formula:

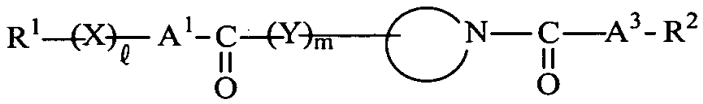


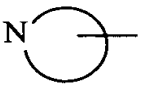
wherein R^1, A^1,  , X, Y, ℓ and m are each as defined above, or its reactive derivative at the amino group or a salt thereof, with a compound of the formula

$$R^2\text{-}A^3\text{-}COOH$$

wherein R^2 and A^3 are each as defined above,

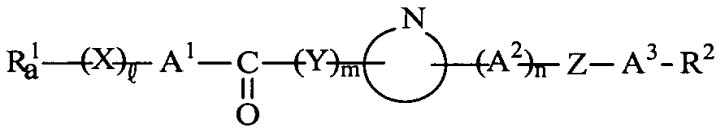
or its reactive derivative at the carboxy group or a salt thereof, to give a compound of the formula:

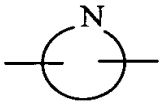


wherein R^1, R^2, A^1, A^3,  , X, Y, Q and m are each as defined above,

or a salt thereof, or

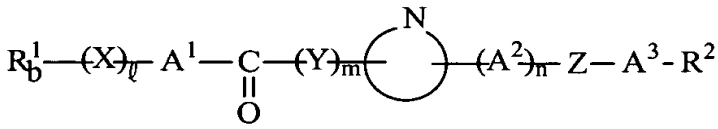
(iv) subjecting a compound of the formula:

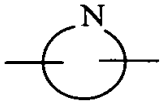


wherein R^2, A^1, A^2, A^3,  , X, Y, Z, ℓ, m and n are each as defined above, and

$R^1{}_a$ is a substituted or unsubstituted N-containing cycloalkyl having amino protective group, [which may have one or more suitable substituent(s)],

or a salt thereof, to elimination reaction of the amino protective group, to give a compound of the formula:

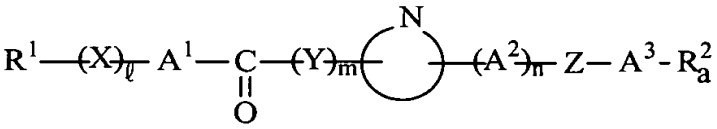


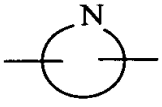
wherein R^2, A^1, A^2, A^3,  , X, Y, Z, ℓ, m and n are each as defined above, and

$R^1{}_b$ is a substituted or unsubstituted N-containing cycloalkyl [which may have one or more suitable substituent(s)],

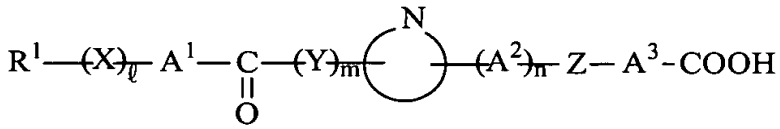
or a salt thereof, or

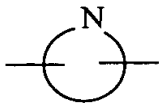
(v) subjecting a compound of the formula:



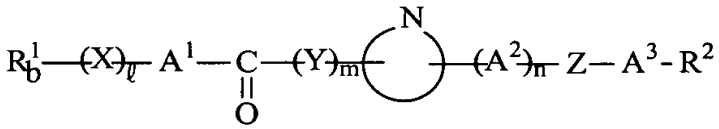
wherein R^1, A^1, A^2, A^3,  , X , Y, Z , ℓ, m and n are each as defined above, and

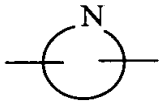
R^2_a is protected carboxy, or a salt thereof, to elimination reaction of carboxy protective group, to give a compound of the formula:



wherein R^1, A^1, A^2, A^3,  , X, Y, Z, ℓ, m and n are each as defined above, or a salt thereof, or

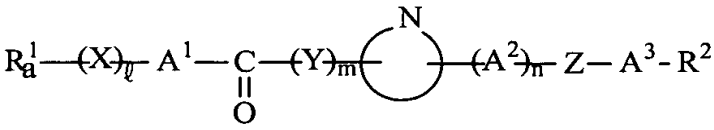
(vi) subjecting a compound of the formula:

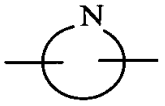


wherein R^2 A^1, A^2, A^3,  , X, Y, Z, ℓ, m and n are each as defined above, and

R^1_b is a substituted or unsubstituted N-containing cycloalkyl [which may have one or more suitable substituent(s)],

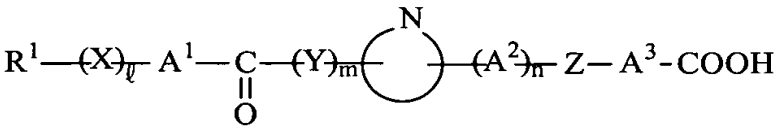
or a salt thereof, to protecting reaction of amino, to give a compound of the formula:

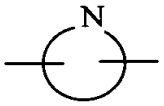


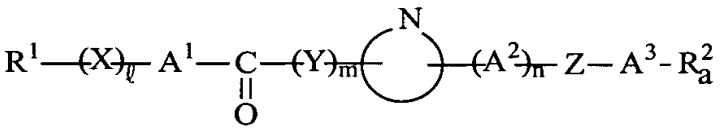
wherein R^2, A^1, A^2, A^3,  , X, Y, Z, ℓ, m and n are each as defined above, and

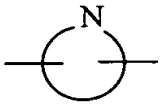
R^1_a is a substituted or unsubstituted N-containing cycloalkyl having amino protecting group, [which may have one or more suitable substituent(s)], or a salt thereof, or

(vii) subjecting a compound of the formula:

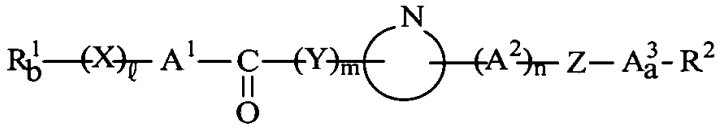


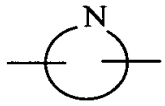
wherein R^1, A^1, A^2, A^3,  , X, Y, Z , ℓ, m and n are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, to protecting reaction of the carboxy, to give a compound of the formula:

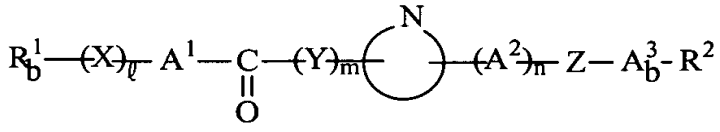


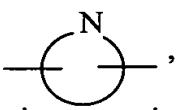
wherein R^1, A^1, A^2 A^3,  , X , Y, Z , ℓ, m and n are each as defined above, and R^2_a is a protected carboxy, or a salt thereof, or

(viii) subjecting a compound of the formula:

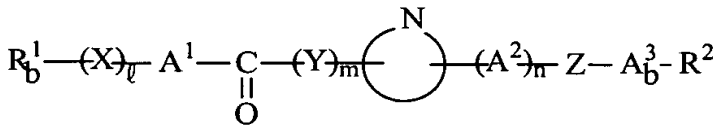


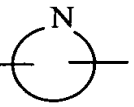
wherein R^1_b, R^2, A^1, A^2,  , X, Y, Z, ℓ, m and n are each as defined above, and A^3_a is lower alkylene having protected amino or a salt thereof, to elimination reaction of amino protective group, to give a compound of the formula:

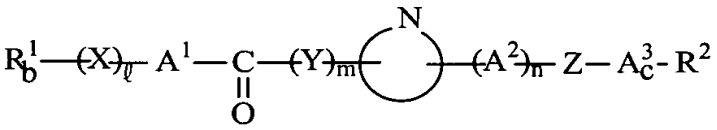


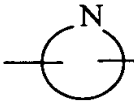
wherein R^1_b, R^2, A^1, A^2,  , X, Y, Z, ℓ, m and n are each as defined above, and A^3_b is a lower alkylene having an amino or a salt thereof, or

(ix) subjecting a compound of the formula:



wherein R^1_b, R^2, A^1, A^2,  , X, Y, Z, ℓ, m and n are each as defined above, and A^3_b is lower alkylene having amino, or a salt thereof, to acylation reaction of amino, to give a compound of formula:

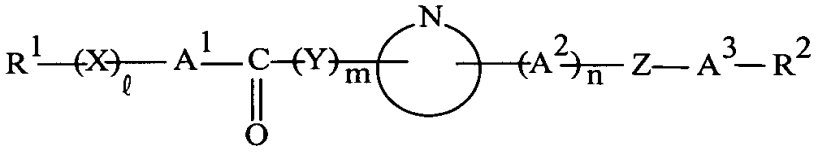


wherein R^1_b, R^2, A^1, A^2,  , X, Y, Z, ℓ, m and n are each as defined above, and A^3_c is lower alkylene having acylamino, or a salt thereof.

16. (Amended) [A] The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound or pharmaceutically acceptable salt thereof is admixed with a pharmaceutically suitable carrier [for use as a medicament].

17. (Amended) A method for the [prevention and/or the] treatment of diseases caused by thrombus formation; restenosis or reocclusion; the thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation or transplantation; disseminated intravascular coagulation; thrombotic thrombocytopenic; essential thrombocytosis; inflammation; [immune diseases; or metastasis] or for the adjuvant therapy with thrombolytic drug or anticoagulant; which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

18. (Amended) A compound of the formula:



wherein:

R^1 is a 6-membered cyclo(lower)alkyl containing 1 to 3 nitrogen atoms which may have one or more amino protective groups;

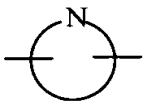
X is O, S or NH, and

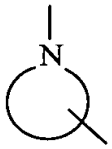
ℓ is an integer of either 0 or 1;

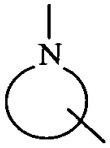
A^1 is a substituted or unsubstituted lower alkylene, a substituted or unsubstituted lower alkenylene or a substituted or unsubstituted lower alkanyl-ylidene [, each of which may have one or more suitable substituent(s)];

Y is NH, and

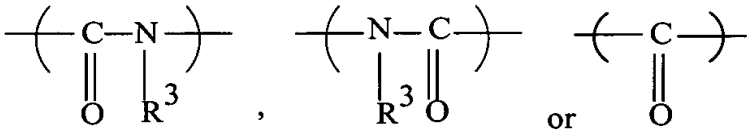
m is an integer of either 0 or 1;

 is a group of the formula:



wherein  is a substituted or unsubstituted 5 or 6-membered N-containing heterocyclic group containing 1 to 3 nitrogen atoms [which may have one or more suitable substituent(s)];

A^2 is a lower alkylene, and n is an integer of either 0 or 1;

Z is  or

wherein R^3 is hydrogen or a lower alkyl;

A^3 is a substituted or unsubstituted lower alkylene [which has one or more suitable substituents];

and R^2 is a carboxy or a protected carboxy;

or a pharmaceutically acceptable salt thereof.

22-38. (New)

22850